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Inflammatory Bowel Disease and Cognitive Behavioural Therapy: a Systematic Review and Meta-analysis

David dos Santos Cardoso

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David dos Santos Cardoso

Orientado por:

Professor Doutor António Diogo Telles Correia

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Abstract

Introduction. Inflammatory bowel diseases (IBDs) are chronic, relapsing-remitting, multifactorial disorders characterized by chronic intestinal inflammation, associated with psychiatric disorders, such as anxiety and depression, and with poorer quality of life. Some trials have reported benefit of cognitive-behavioural therapy (CBT) for these patients.

Aim. In this review, we aim to summarize and analyse the evidences of CBT in IBD patients regarding disease activity, anxiety, depression and quality of life.

Methods. Randomized controlled trials recruiting patients with IBD that compared CBT to a control group were included, regardless of age or date of publication. Search was performed on MEDLINE, and additional trials were selected from grey literature and references from selected articles. Any disease-related or psychological outcomes were considered for the systematic review, and data regarding disease activity, anxiety, depression and quality of life was included in the meta-analysis. We summarized the findings using descriptive statistics, including mean and standard deviation (SD) scores for outcomes of interest. Generic inverse variance with random-effects models were run to obtain effect estimates expressed as standardized mean difference (SMD) and 95% confidence intervals (CIs).

Results. We identified 117 studies of which 11 studies included, with a total of 1012 participants. None of the outcomes reported benefit from CBT. Disease activity was evaluated in 7 trials, with 2 included in our analysis showing no improvement (SMD: 0.060; -0.449 0.568 CI 95%; p-values>0.818). Depression (SMD: -0.131; -0.347, 0.084 CI 95%; p-values>0.233) was evaluated in all trials, anxiety (SMD: -0.029; -0.232, 0.173 CI 95%; p-values>0.777) and quality of life (SMD: 0.037; -0.178, 0.252 CI 95%; p-values>0.736) in 7, with 3 included in our analysis showing no improvement.

Discussion and conclusion. This meta-analysis failed to prove that CBT could be of benefit for IBD patients on 4 major outcomes: disease activity, depression, anxiety and quality of life, but several limitations were found. Future studies should include more patients, perform subgroups analysis, and adequately report data.

Keywords. IBD, CBT, depression, QoL

Resumo

Introdução. As doenças inflamatórias do intestino (DII) são doenças crónicas, com agudizações, multifactoriais, caracterizadas por inflamação crónica do intestino e estão associadas a perturbações psiquiátricas, como depressão e ansiedade, assim como uma pior qualidade de vida. Alguns estudos reportaram benefício com a aplicação de terapia cognitivo-comportamental (TCC) nestes doentes. **Objectivo.** Nesta revisão, propomo-nos inventariar e analisar as evidências da TCC nos doentes com DII relativas à actividade da doença, depressão, ansiedade e qualidade de vida (QdV).

Métodos. Foram incluídos estudos controlados e aleatorizados que compararam TCC com um grupo controlo, independentemente da idade ou data de publicação. A pesquisa foi efectuada na MEDLINE, e estudos adicionais foram selecionados da literatura cinzenta e da bibliografia de estudos seleccionados. Todos os outcomes foram considerados para a revisão sistemática, e os dados relativos a actividade da doença, depressão, ansiedade e qualidade de vida foram incluídos na meta-análise. Dados foram resumidos em médias e desvios-padrão (DP). Variância inversa genérica com modelos de efeitos aleatorizados foram feitas para obter estimativas do efeito, expressas em diferenças de médias padronizadas (DMP) com intervalos de confiança de 95% (IC).

Resultados. Identificámos 117 estudos, dos quais 11 foram incluídos na revisão sistemática, com um total de 1012 doentes. Nenhum outcome demonstrou benefício da TCC. A actividade da doença foi avaliada em 7 estudos, tendo 2 sido incluídos na nossa análise (DMP: 0.060; -0.449 0.568 IC 95%; p-values>0.818). A depressão (DMP: -0.131; -0.347, 0.084 IC 95%; p-values>0.233) foi avaliada em todos os estudos, a ansiedade (DMP: -0.029; -0.232, 0.173 IC 95%; p-values>0.777) e qualidade de vida (DMP: 0.037; -0.178, 0.252 IC 95%; p-values>0.736) em 7, com 3 incluídas na nossa análise, não tendo sido demonstrado benefício. **Discussão e conclusão.** Esta meta-análise falhou em provar benefícios da TCC nos doentes com DII nos 4 outcomes principais: actividade da doença, depressão, ansiedade e qualidade de vida, mas foram encontradas grandes limitações. Estudos futuros deverão incluir mais doentes e fazer análises de subgrupo, reportando dados completos.

Palavras-chave. **DII, TCC, depressão, QdV**

O trabalho final exprime a opinião do autor e não da FML.

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Introduction

Inflammatory bowel diseases (IBDs) are chronic, relapsing-remitting, multifactorial disorders comprising two major diseases – Crohn's Disease (CD) and Ulcerative Colitis (UC) –, characterized by chronic relapsing intestinal inflammation. Their prevalence values range from 249 to 505 per 100 000 persons for UC, and 319 to 322 per 100 000 persons for CD, in Europe and North America, respectively, with increasing worldwide incidence[1].

Although of unknown aetiology, genetics, environment, intestinal microbial flora and immune system are involved in their pathogenesis[2–4], making the immune system the main target of their treatment[5].

Association between IBDs and psychiatric disorders have been reported, mainly anxiety and depression[6–8], with a suggested bidirectional path[9,10]. Also, a poorer quality of life (QoL), has been reported[11,12]. Psychotherapeutic strategies have been used, such as psychodynamic psychotherapies, hypnotherapy, self-management therapies, mindfulness and cognitive-behavioural therapies (CBT), but evidence is not clear, though CBT seems to have some benefit on depression and QoL at short-term[13–16].

Initially developed for depression, CBT has been used in patients with irritable bowel syndrome, with evidence proving it to be a first-line treatment in these patients[17]. Through a similar brain-gut axis, it was proposed to work on IBDs patients. CBT in IBDs patients has been focusing on disease education, relaxation techniques, training coping strategies, improving social skills, and introducing cognitive restructuring, though there is no single protocol for these diseases[17,18].

In this review, we aim to summarize the evidence of all randomised controlled trials of CBT in patients with IBDs, establishing benefits for patients' management through a meta-analysis – regarding benefits of CBT in IBDs disease activity, anxiety, depression and quality of life –, and pointing directions for future trials.

Methods

Eligibility criteria

In this systematic review, all published controlled clinical trials were considered which investigated the effects of CBT on patients diagnosed with IBD, had a control group, and with no restriction of age. Any disease-related or psychological outcomes, quantitative or qualitative were considered. There was no restriction to publication date or language.

Information sources

According to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[19], studies were identified by searching "Inflammatory bowel disease" AND "Cognitive-behavioural therapy" in Titles/Abstracts on MEDLINE on 4 and 16 May, 2018. To avoid the risk of missing relevant articles, additional papers were searched on the grey literature (i.e. generic web search) and through the bibliography of previous reviews.

Study selection

One author (DdS) ran the search and screened the initial titles after duplicates removed. Two authors (DdS and DTC) independently examined potential relevant articles in depth, using the following criteria as defined by PICO model[19]: (i) population: subjects affected by IBD; (ii) intervention: CBT; (iii) comparator: no intervention (i.e. wait-list control group) or treatment as usual; (iv): outcomes: disease activity, anxiety, depression and quality of life. Trials meeting eligibility criteria were included, after full-text assessment. Disagreements between authors were solved in a consensus meeting.

Data collection

Data was extracted by DdS, using a standardized extraction sheet. Missing or additional data as requested from the studies' first author. From each trial were extracted: first author's name, year of publication, number of participants (total, treatment group, control group), age of participants, control group details, whether there was a psychological screening or not, outcomes (any, disease-related or psychological), duration of treatment,

duration of follow-up, dropout rate, main findings and study design features. Means and standard deviations for disease activity, anxiety, depression and quality of life were extracted and included in the meta-analysis.

Data synthesis and analysis

We summarized the findings using descriptive statistics, including mean and standard deviation (SD) post-intervention scores for outcomes of interest. Generic inverse variance with random-effects models were run in Review Manager 5.3.5[20] to obtain effect estimates expressed as standardized mean difference (SMD) and their accompanying 95% confidence intervals (CIs). By convention, a SMD of 0.20 is considered small, 0.50 medium, and ≥0.80 a large effect[21].

Heterogeneity of studies was addressed by the estimation of τ^2 and I^2, considering an I^2 value <40% as an indicator of marginal heterogeneity[22].

Assessment of risk of bias in included studies

Risk of bias was assessed with Cochrane risk of bias tool[22]. All trials were screened for random sequence generation (Selection bias), allocation concealment (selection bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias). Disagreements between authors were solved in a consensus meeting.

Results

After database and references search, 117 studies were found. Title and abstracts were searched and 103 were excluded because they didn't meet inclusion criteria. Full text of 14 studies[23–36] were screened, and 3 were excluded (1[26] was an open trial, 1[28] didn't have a control group, and 1[27] wasn't a CBT-based trial). A total of 11 studies were analysed and included in this review. A flow diagram based on PRISMA statement[19] is shown on figure 1. A summary of analysed studies is present on table 1.

Participants

A total of 1012 participants integrated these studies, of which 443 of paediatric age (8-17 years old). A total of 673 presented Chron's disease and 330 ulcerative colitis (9 unspecified). All studies did psychological screening, most excluding severe mental diseases like major depression, psychotic disorders, and substance or alcohol abuse, and patients on psychological treatment. One study[31] was performed specifically in depressed patients, 1[29] in subsyndromal depressive patients, and 1[25] in poor mental health-related quality of life patients. Most studies didn't report disease activity in inclusion/exclusion criteria, though 1[32] included only patients in remission/mild symptoms, and other[34] excluded severe disease.

Treatment characteristics

Most studies performed 1-2h/week manual-based CBT sessions for 8-12 weeks. One[34] study was a computerized based CBT trial, and another[32] also offered this option. One[36] study used a brief CBT approach of 1h session/week, for 3 weeks. Sessions usually focused on disease information, relaxation techniques, coping strategies, social skills and cognitive restructuring.

Outcomes assessed and main findings

Disease activity[23,31–36]

Seven studies assessed disease activity, using the number of symptoms, and PCDAI, PUCAI, CDAI and SSCAI. One[23] found CBT to be detrimental (though underpowered and with severe risk of bias); 3[32,34,35] found no effects; 1[31] found lessened disease activity posttreatment in youth, with a subgroup[33] analyses of CD patients with the same result; 1[36] found a reduction in the number of flares for a subgroup analyses of patients with 2 or more previous flares.

Complete data on disease activity was obtained from 2[32,34] studies, with a total of 242 CD patients and 123 UC patients included in our analysis; 132 and 65 were allocated to the intervention group, 100 and 58 to the control group, for CD and UC respectively. We found no significant effect of CBT on disease activity (SMD: 0.060; -0.449 0.568 CI 95%;

p-values>0.818). Forest plots summarizing findings from meta-analysis are shown in Figure 2.

Depression[23-25,29–36]

All studies assessed depression/depressive symptoms through BDI, SCL-90-R, HADS, CDI, CDRS-R and CESDS. Six[31–36] studies found no improvement; improvement was reported in 5[23–25,29,30] studies – 1[29] study found only a posttreatment improvement, not significant at follow-up; in a subgroup[30] analyses of the previous study, CD patients not medicated with systemic steroids, depression symptoms improved even at follow-up.

Complete data on disease activity was obtained from 3[32,34,36] studies, with a total of 558 patients included in our analysis; 294 were allocated to the intervention group and 264 to the control group. We found no significant effect of CBT on depression (SMD: -0.131; -0.347, 0.084 CI 95%; p-values>0.233). Forest plots summarizing findings from meta-analysis are shown in Figure 3.

Anxiety[23–25,32,34–36]

Seven studies assessed anxiety with STAI, SCL-90-R, HADS and MASC. Five[23,25,32,34,35] found no improvement; 2[24,25] found significant improvements.

Complete data on disease activity was obtained from the same 3[32,34,36] studies. We found no significant effect of CBT on anxiety (SMD: -0.029; -0.232, 0.173 CI 95%; p-values>0.777). Forest plots summarizing findings from meta-analysis are shown in Figure 4.

Health-related quality of life[25,31–36]

HRQoL was assessed in 7 studies with IMPACT III questionnaire, SF-36, SF-12 and IBDQ. Three[31,33,35] reported no improvement; 1[32] reported improvement in a subgroup analyses (younger patients, high baseline IBD activity, recently diagnosed, poor coping and high anxiety/depression scores on HADS) at 6 months, which was lost at 24 months;

2[34,36] found only posttreatment improvement; and 1[25] found improvement in mental aspects of QoL and IBD-related QoL.

Complete data on disease activity was obtained from the same 3[32,34,36] studies. We found no significant effect of CBT on QoL (SMD: 0.037; -0.178, 0.252 CI 95%; p-values>0.736). Forest plots summarizing findings from meta-analysis are shown in Figure 5.

Other findings

Coping strategies were evaluated in 4[32,34–36] studies, with 2[32,35] reporting no differences, 1[34] reporting CBT to significantly decrease less in religion score, more in substance abuse score, and increased more in venting score in brief COPE, and 1[36] reporting reduction in parents' solicitousness, parent reported child problem-focused coping and child reported catastrophizing posttreatment and at 12 months. Also, 1[36] study reported a reduction in number of missed school days for children at 6 months, which was lost at 12 months.

Risk of bias

Risk of bias was assessed with Cochrane risk of bias tool[22], and is shown on table 2.

Discussion

This meta-analysis failed to prove that CBT could be of benefit for IBD patients on 4 major outcomes: disease activity, depression, anxiety and quality of life.

As said, IBD is associated with psychiatric disorders as depression[6–8], and CBT has been successfully used in other gastrointestinal disorders such as irritable bowel syndrome, so it was expected that CBT would be effective in reducing depressive symptoms. It is probable that psychiatric disorders in IBD patients would have a higher organic component compared to IBS patients, according to what we know from their physiopathology, which could help to explain the lack of effectiveness demonstrated in this analysis; this has even a higher importance in disease activity outcomes.

There were several limitations on data reporting and collecting; of a total of 1012 participants, only 365 were evaluated for disease activity, 558 for depression, anxiety and QoL. Future studies with a higher number of participants, and with complete data report would endorse evidences.

A study[32] has suggested that subgroups of IBD patients, such as younger patients, high baseline IBD activity, recently diagnosed individuals, poor coping and high anxiety/depression symptoms, could benefit more from CBT, which should be explored in future studies. In this study, QoL significantly improved at 6 months. One study[29], conducted in subsyndromal depressed adolescents, depressive symptoms were significantly reduced in CBT treated patients at short-term; other[25], conducted in selected poor mental health QoL patients, reported significant in improving in IBD-related QoL, mental aspects of general QoL, anxiety and depression symptoms. These findings suggest that a IBD patients' subgroup could benefit from this intervention, which needs to be assessed in future trials.

Most studies indiscriminately included patients with both active and inactive disease. It needs to be clarified, in the future, if there are differences on these subgroups. Subgroup analyses for all outcomes should also be performed for CD and UC patients separately. Treatment schemes, especially regarding to corticosteroids and other mental health interfering drugs should also be reported and taken into account when analysing CBT benefits.

Regarding intervention characteristics, as most studies only reported short-time benefits lost in time, booster sessions may improve effectiveness of CBT as some[30,34,36] have suggested.

High dropout rates may be due to CBT characteristics, as this treatment is highly time demanding. This is a serious issue in most of the trials and should be addressed in the future. Analysing which components of CBT would be of most benefit could bring new insights. One study has already addressed this issue, but data is insufficient for a conclusion. A CBT-based approach focusing on these future findings could be less time-consuming and reduce dropout rates. Being relatively unknown diseases for non-health related population, we suggest that focus on disease education should not be lost. Also, the role of computerized CBT should be established, regarding which patients were able to most benefit from it, specially attending to the acceptance of technology delivered

therapies, which may differ for different cultures. Comparing different CBT protocols is another main limitation of this study, as several different protocols have been used, which may produce different results; this emphasizes the need of creating a single protocol for these patients.

The elevated number of outcomes assessed (and questionnaires answered) in some studies could also have contributed to high dropout rates. We suggest that future studies should focus mainly on disease activity, depression, anxiety and QoL. Quality of life is of particular importance as it is one of the main goals of all treatments, and improvements in other outcomes may not be reflected in a higher quality of life. In fact, if physiopathology of these diseases is considered, we do not expect that disease activity would be significantly reduced after CBT. Also regarding questionnaires, we should remember that most scales used for depression and anxiety were built for non-medical patients, and physical symptoms included in these scales are symptoms already presented in IBD patients, which may skew results. HADS should be the preferred scale for these patients.

None of the studies reported analyses of treatment's costs, which should also be assessed, as only marginal benefits may not be economically sustainable.

Conclusions

Though this meta-analysis failed to prove benefit from CBT for IBD patients, due to the association of psychiatric disorders on this population, we believe that future studies will bring evidence favouring this treatment, especially in the suggested subgroups. Particular attention should be on depression symptoms and quality of life. In nowadays practice, only patients with psychopathology of relevance should be considered for a CBT intervention; additionally, patients from described subgroups can also be appointed for CBT, after a careful, integrative and personalized evaluation.

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Figures

Figure 1 Study selection diagram

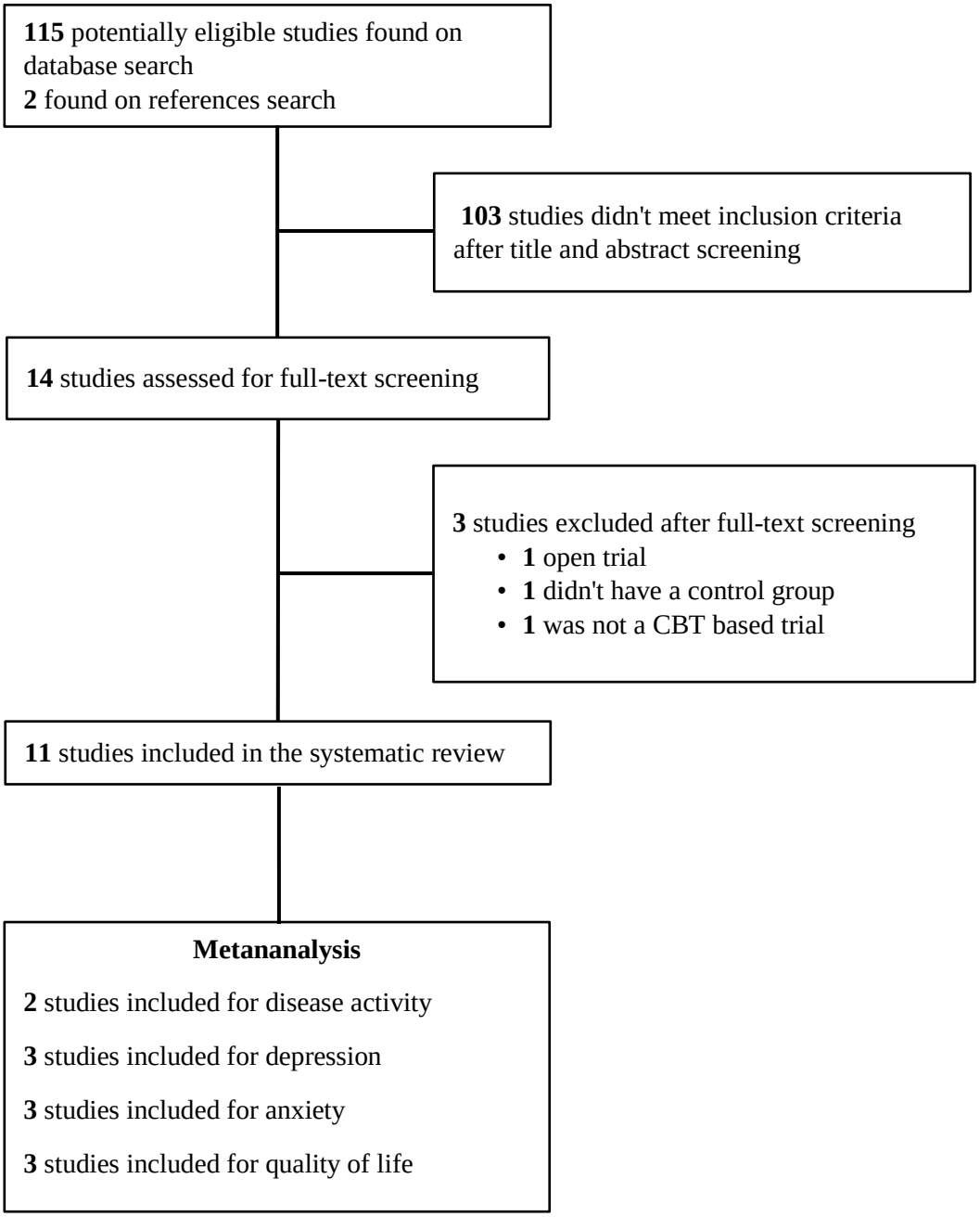


Figure 2 Disease activity in IBD patients

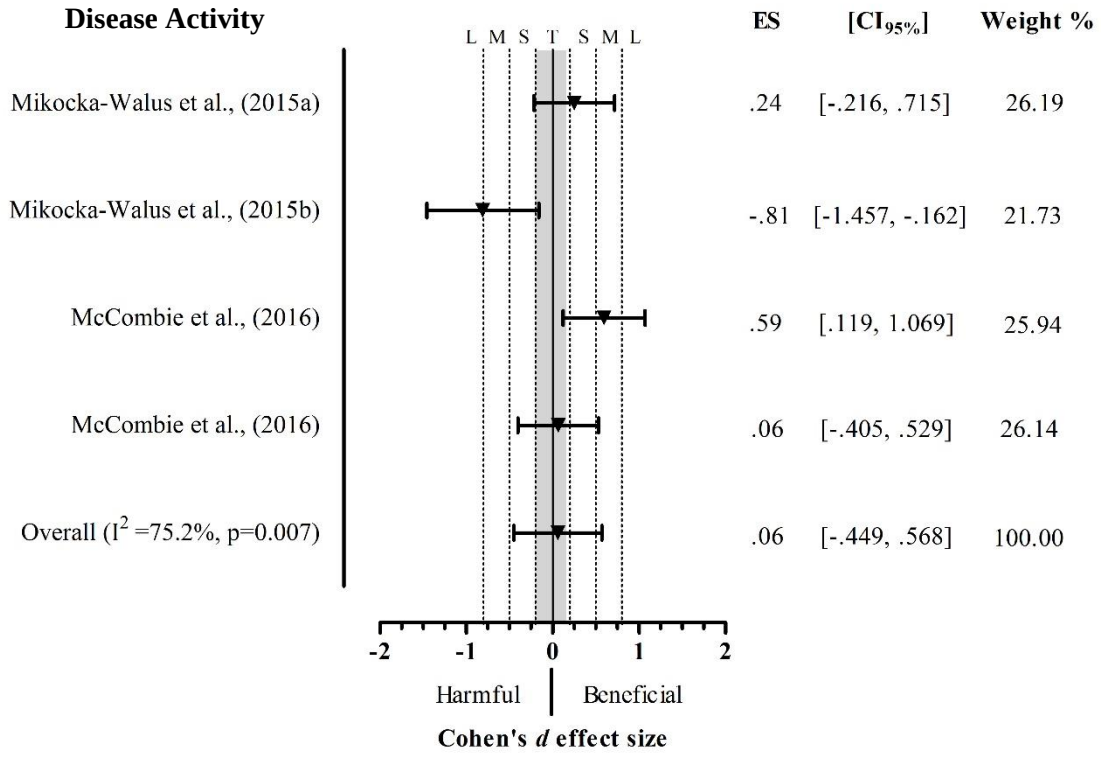


Figure 3 Depression in IBD patients

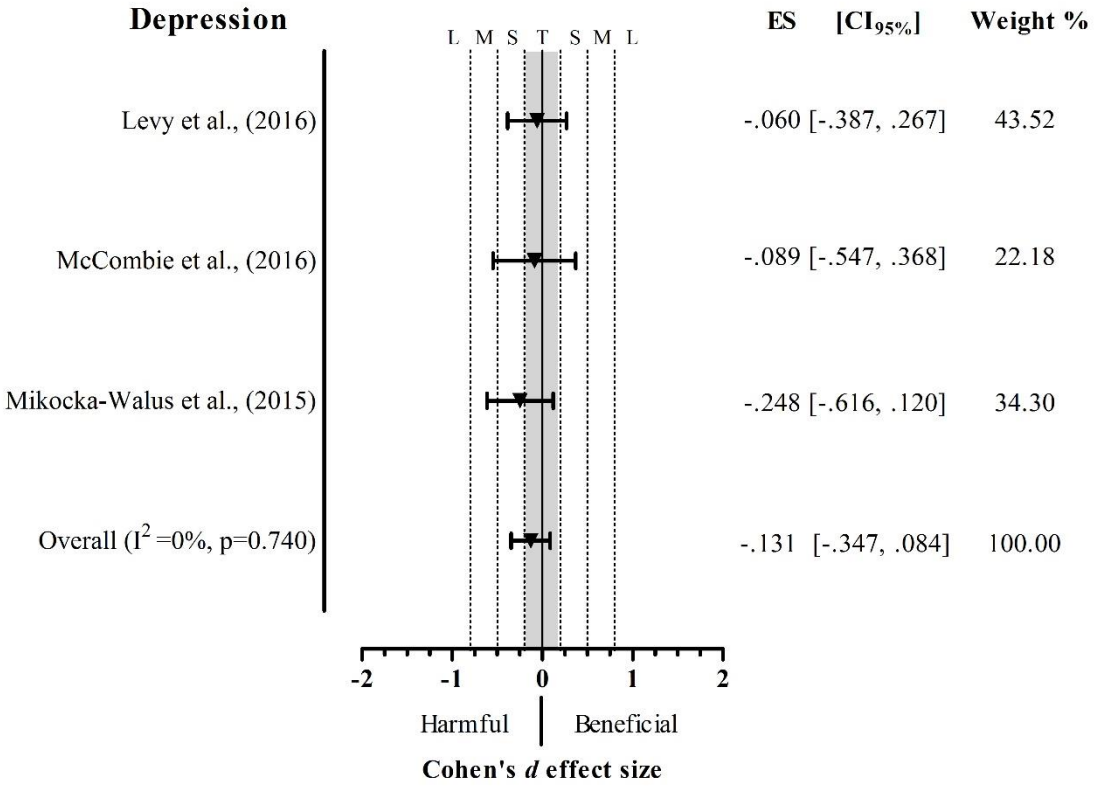


Figure 4 Anxiety in IBD patients

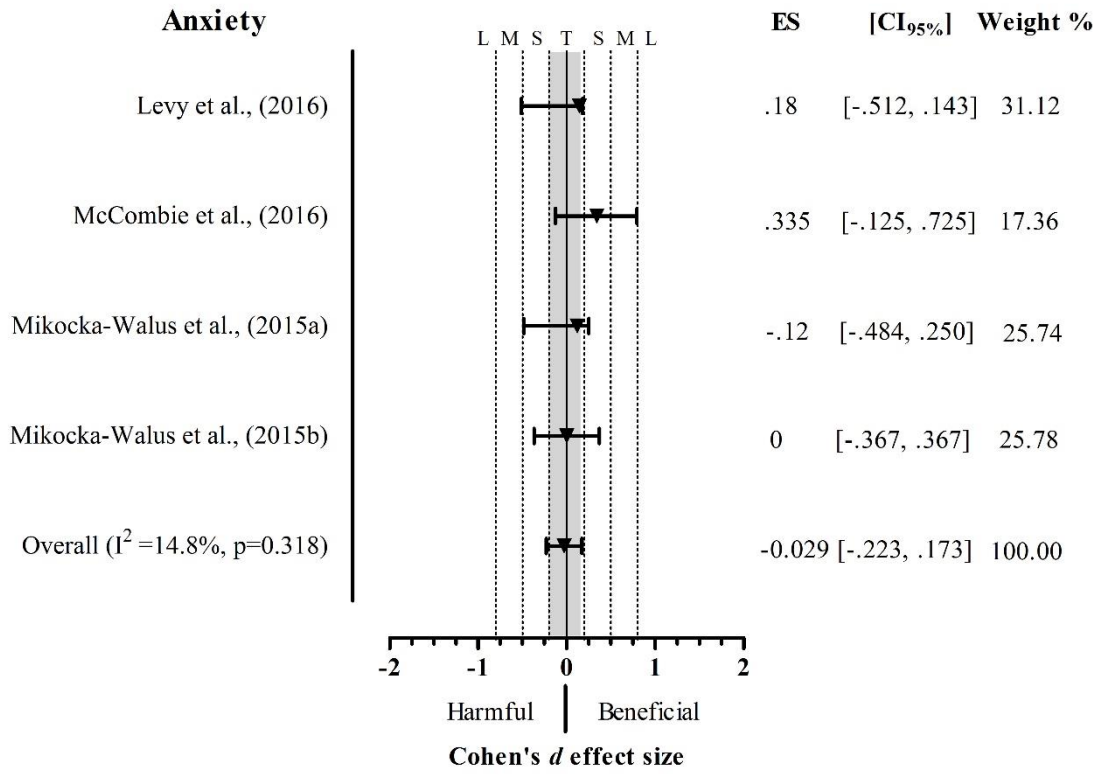
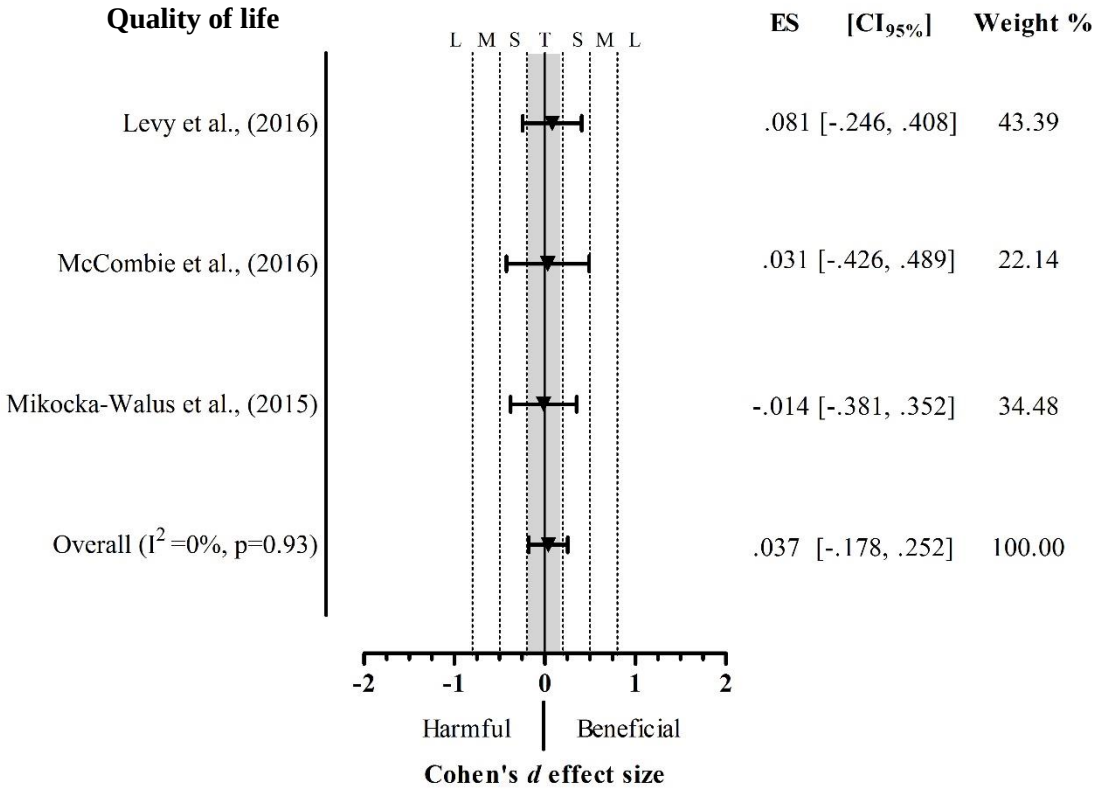


Figure 5 Quality of life in IBD patients



Tables *Table 1 Controlled CBT trials for IBD: characteristics of included studies*

First Author, year	No. Participants	Treatment group, *n*	Control group, *n*	Age, years (mean)	Psychological screening	Outcomes
Schwatz, 1991[23]	21	11 (7 CD, 3 UC, 1 NA)	10 (3 CD, 7 UC) (Symptom Monitoring)	25-71 (43)	Yes; major depressive episode, bipolar disorder, schizophrenia excluded.	Symptoms (Abd. Pain, malaise, diarrhoea, anorexia, nausea, abd. distension, urge. defecate, urge. urinate), depression (BDI), anxiety (STAI), psychosomatic symptoms (PSC), disease related stress (IBD index), HS, LES.
Sibaja, 2007[24]	57 (34 CD; 23 UC)	33	24 (Waiting list)	>18	Yes; severe psychological rates on SCL-90-R, BDI, HAD excluded.	Depressive or anxiety symptoms on SCL-90-R, BDI, HADS.
Szigethy, 2007[29] Thompson, 2012[30] (follow-up)	41	22 (15 CD, 7 UC)	19 (14 CD, 5 UC) (TAU)	11-17 (14,99)	Yes; with CDI-CP. Major depressive, dysthymic, bipolar and psychotic disorders excluded.	Psychiatric diagnoses (No. of K-SADS), depressive severity (CDI-CP), cognitive processing (PCSC) and global functioning (CGAS).
Szigethy, 2014[31] Szigethy, 2015[33] (CD subgroup)	217 (161 CD; 56 UC)	110	107 (Supportive non-directive therapy)	9-17 (14,3)	Yes; with CDI-CP and K-SADS. Major/minor depression included. Bipolar, psychotic and eating disorders and substance abuse excluded.	Depression severity (CDRS-R), health-related adjustment (IMPACT-III questionnaire, CGAS), and IBD activity (PCDAI, PUCAI).
Mikocka-Walus, 2015[32] Mikocka-Walus, 2017[35] (24 months follow-up)	174	90 (58 CD, 32 UC)	84 (49 CD, 35 UC) (Standard Care)	>18	Yes; clinical psychologist diagnoses of serious mental illness (psychosis, schizophrenia and substance abuse) excluded.	IBD remission (CDAI, SSCAI), HRQoL (SF-36), depression (HADS), anxiety (STAI, HADS), coping (brief COPE, IBDSCCQ), stress (RSRRS).
McCombie, 2016[34]	199	113 (75 CD, 34 UC, 4 unsp.)	86 (62 CD, 20 UC, 4 unsp.) (TAU)	18-65	Yes; psychotic disorder and alcohol and substance abuse excluded	HRQoL (IBDQ, SF-12), anxiety/depression (HADS), stress (PSS-10), social functioning (SFQ), neuroticism (EPQ-BF), coping (brief COPE), disease activity (SSCAI, HBI).
Levy, 2016[36]	185	91 (67 CD, 24 UC)	94 (60 CD, 34 UC) (Educational support)	8-17 (13,5)	Yes; developmental disabilities requiring full-time special education and impairing ability to communicate excluded	Process variables: parents response to pain behaviour (ARCS), pain coping skills and believes (PRI, PBQ). Outcome variables: healthcare utilization (disease-related hospitalizations and no. of visits to healthcare providers), school attendance, QoL (IMPACT III questionnaire), depressive symptoms (CDI), anxiety (MASC), general activity limitations (FDI), disease activity (no. of flares).
Evertsz', 2017[25]	118	59 (35 CD, 24 UC)	59 (33 CD, 26 UC) (Waiting list)	17-76 (39)	Yes, with SCID-I; substance abuse, bipolar and psychotic disorders excluded. Poor mental health QoL was an inclusion criterion (assessed through SF-36).	HRQoL (IBDQ), depression and anxiety (HADS, CESDS), general health (SF-36).

(continued)

First Author, year	Treatment	Duration of treatment/follow-up	Dropouts (n/%)	Main findings
Schwatz, 1991[23]	Disease information, relaxation techniques, thermal biofeedback, coping strategies	1h sessions 8 weeks (12 sessions) 3 months	2 (from control group)	Psychological treatment was overall detrimental on symptoms control. Abdominal pain was the only statistically significant symptom decreasing on treatment group; this was lost at follow-up. IBD index score decreased on treatment group.
Sibaja, 2007[24]	Manual-based group CBT. Disease information, relaxation techniques, coping strategies, social skills, cognitive restructuring	2h session/week, 10 weeks 12 months	?	Significant posttreatment improvement on all outcomes and at 12 months follow-up.
Szigethy, 2007[29] Thompson, 2012[30] (follow-up)	PASCET-PI (manual-based CBT). Disease information, illness narrative, relaxation techniques, coping strategies, social skills, cognitive restructuring.	1h session/week, 9-12 weeks 12 months	11	Significant posttreatment reduction in depressive severity, global functioning, self-reported perceived control. At follow-up, reduction in depressive severity was not significant; global functioning improved significantly. PSCS was not measured. For CD patients' subgroup, similar results were found. When youth on systemic steroids were excluded, CBT reduced depression severity significantly. *(Study conducted on subsyndromal depressed adolescents.)*
Szigethy, 2014[31] Szigethy, 2015[33] (CD subgroup)	PASCET-PI	45min session/week, 12 weeks ---	29,5%	Both psychotherapies were associated with reduced depression severity, improved health-related adjustment, and lessened IBD activity. Only the last was significant, favouring CBT. *(Study conducted on depressed youth, comparing CBT to SNDT.)*
Mikocka-Walus, 2015[32] Mikocka-Walus, 2016[35] (24 months follow-up)	Disease information, relaxation techniques, coping strategies, social skills, cognitive restructuring	2h session/week, 10 weeks 12 months 24 months	39,7% (12 months) 57,4% (24 months)	Compared to SC, CBT wasn't better in any outcome assessed. In a subgroup analyses (younger patients, high baseline IBD activity, recently diagnosed, poor coping and high anxiety/depression scores on HADS), CBT was effective in improving QoL at 6 months. No differences between SC and CBT were found at 24-months follow-up
McCombie, 2016[34]	Computerized CBT. Relaxation techniques, coping strategies, social skills, cognitive restructuring.	1 online session/week, 8 weeks 6 months	48,5%	CBT was associated with better HRQoL posttreatment but not at 6 months. ITT analyses did not confirm this. At 6 months, CBT significantly decreased less in religion score, more in substance abuse score, and increased more in venting score in brief COPE.
Levy, 2016[36]	Coping strategies, stress management, cognitive restructuring for children and parents	70 min session/week, 3 weeks 12 months	?	There was a significant reduction in parents' solicitousness, parent reported child problem-focused coping and child reported catastrophizing posttreatment and at 12 months. There was a non-maintained posttreatment improvement in QoL and a significant reduction in the no. of missed school days only at 6 months. Though underpowered, a subgroup analyses revealed a significant reduction in no. of flares for those who had 2 or more flares ad initio.
Evertsz', 2017[25]	Manual-based CBT Disease education, cognitive restructuring.	1h session/week, 8 weeks 3,5 months	18,6%	CBT was significant in improving IBD-related QoL, mental aspects of general QoL, and anxiety and depression symptoms. *(Study conducted on poor mental health QoL IBD patients.)*

Notes:
ARCS – Adults' Responses to Children's Symptoms; **BDI** – Beck Depression Inventory; **CBT** – Cognitive Behavioural Therapy; **CD** – Crohn's Disease; **CDAI** – Crohn's Disease Activity Index; **CDI-CP** – Children's Depression Inventory, Child and Parent report; **CDRS-R** – Children's Depression Rating Scale – Revised; **CESDS** – Centre for Epidemiologic Studies – Depression Scale; **CGAS** – Children's Global Assessment Scale; **COPE** - Coping Operations Preference Enquiry; **EPQ-BF** – Eysenck Personality Questionnaire – Brief Version; **FDI** – Functional Disability Inventory; **HADS** – Hospital Anxiety and Depression Scale; **HBI** – Harvey-Bradshaw Index; **HRQoL** – Health-related Quality of Life; **HS** – Hassless Scale; **IBD Index** – Inflammatory Bowel Disease Stress Index; **IBDQ** – IBD Questionnaire; **IBDSCCQ** – IBD Stages of Change Coping Questionnaire; **ITT** – Intention To Treat; **K-SADS** – Schedule for Affective Disorders and Schizophrenia for School-Age Children; **LES** – Life Events Scale; **MASC** – Multidimensional Anxiety Scale for Children;

PASCET-PI – Primary and Secondary Control Enhancement Therapy – Physical Illness; **PBQ** – Pain Beliefs Questionnaire; **PCDAI** – Pediatric Crohn's Disease Activity Index; **PCSC** – Perceived Control Scale for Children; **PRI** – Pain Response Inventory; **PSC** – Psychosomatic Symptom Checklist; **PSS-10** – Perceived Stress Scale, 10-item version; **PUCAI** – Pediatric Ulcerative Colitis Activity Index; **QoL** – Quality of Life; **RSRRS** – Revised Social Readjustment Rating Scale; **SC** – Standard Care; **SCID-I** – Structured Clinical Interview for DSM IV Axis I-Disorders; **SF-36/SF-12** – Health Status Questionnaire Short Form-36; **SFQ** – Social Functioning Questionnaire; **SCL-90-R** – Symptom Checklist (Anxiety and Depression Scales); **SSCAI** – Simple Clinical Colitis Activity Index; **STAI** – State-Trait Anxiety Inventory; **TAU** – Treatment As Usual; **UC** – Ulcerative colitis; **NA** – Not Available; **Uns.** – unspecified; **Y** – Years.

Table 2 Risk of bias assessment

First Author, year	Random sequence generation (Selection bias)	Allocation concealment (Selection bias)	Blinding of outcome assessment (Detection bias)	Incomplete outcome data (Attrition bias)	Selective reporting (Reporting bias)
Schwatz, 1991	?	-	-	?	-
Sibaja, 2007	?	?	+	?	?
Szigethy, 2007	?	?	+	+	?
Thompson, 2012	?	?	+	?	?
Szigethy, 2014	+	?	+	?	+
Mikocka-Walus, 2015	+	+	?	+	+
Szigethy, 2015	?	?	?	?	?
McCombie, 2016	+	-	-	?	+
Mikocka-Walus, 2016	+	+	?	+	+
Levy, 2016	+	?	?	+	+
Evertsz', 2017	+	?	?	+	+

Apendix

Resumo

Introdução. As doenças inflamatórias do intestino (DII) são doenças crónicas, com agudizações, multifactoriais, englobando duas entidades principais – doença de Crohn (CD) e colite ulcerosa (UC) –, caracterizadas por inflamação crónica do intestino. Na Europa, a prevalência destas doenças situa-se em 249 por 100 000 pessoas para a UC e 319 por 100 000 para CD, com incidência mundial crescente.

Apesar de ter etiologia desconhecida, vários factores estão implicados na sua patogénese, como factores genéticos, ambientais, relacionados com o microbioma intestinal e o sistema imunitário.

A associação em as DII e perturbações psiquiátricas tem sido reportada, principalmente perturbações depressivas e ansiosas, assim como uma pior qualidade de vida (QdV). Estratégias psicoterapêuticas têm sido usadas nestes pacientes, como terapias dinâmicas, hipnoterapia, terapias de auto-gestão de sintomas, tipo mindfulness e terapias cognitivo-comportamentais (TCC). As evidências relativas aos benefícios destas terapias não é clara, mas parece existir benefício da TCC na depressão e QdV a curto-prazo.

A existência de uma relação estreita entre o sistema digestivo e a psique já foi extensamente documenta. Neste sentido, a TCC, tendo sido desenvolvida para a depressão, tem demonstrado resultados positivos doentes com síndrome do cólon irritável, reforçando as provas deste eixo. Foi, por isso, testada em pacientes com DII, focando-se em estratégias educativas para a doença, técnicas de relaxamento, estratégias de coping e restruturação cognitiva.

Objectivo. Nesta revisão, propomo-nos inventariar e analisar as evidências da TCC nos doentes com DII relativas à actividade da doença, depressão, ansiedade e qualidade de vida (QdV), apontando direcções para investigações futuras.

Métodos. Foram incluídos todos os estudos controlados e aleatorizados que compararam TCC com um grupo controlo em doentes com DII, independentemente da idade ou data de publicação. A pesquisa foi efectuada na MEDLINE, recorrendo a termos como "Inflammatory bowel disease" E "Cognitive-behavioural therapy", pesquisados nos

títulos e resumos, e estudos adicionais foram selecionados da literatura cinzenta e da bibliografia de estudos seleccionados. Depois de excluídos duplicados, aos artigos selecciados de acordo com os critérios de inclusão foi extraído o nome do primeiro autor, ano de publicação, número de participantes (total, sob TCC, e controlo), idade dos participantes, características dos grupos controlo, características da intervenção, dados sobre rastreio psicológico, outcomes, duração do tratamento, duração do follow-up, taxa de abandono e resultados principais. Todos os outcomes foram considerados para a revisão sistemática, e os dados relativos a actividade da doença, depressão, ansiedade e qualidade de vida (médias e desvios-padrão) foram incluídos na meta-análise. Resumimos os dados através de estatísticas descritivas, incluindo médias e desvios-padrão (DP) pós-intervenção para estes outcomes. Variância inversa genérica com modelos de efeitos aleatorizados foram feitas para obter estimativas do efeito, expressas em diferenças de médias padronizadas (DMP) com intervalos de confiança de 95% (IC).

Resultados. Identificámos 117 estudos, dos quais 11 foram incluídos na revisão sistemática, com um total de 1012 doentes, dos quais 443 em idade pediátrica (8-17 anos). Seiscentos e setenta e três apresentavam doença de Crohn e 330 colite ulcerosa (9 doença indeterminada). Todos os estudos fizeram rastreio psicológico, Excluindo, a maioria, patologia psiquiátrica severa como depressão, perturbações psicóticas e de abuso de álcool e outras substâncias. Um estudo foi efectuado em doentes com síndrome depressivo, um em doentes com síndrome subdepressívo e um terceiro em doentes com qualidade de vida relacionada a saúde mental reduzida.

A maioria dos tratamentos incluía uma sessão de 1-2h/semana de TCC por 8-12 semanas, focando estratégias educativas para a doença, técnicas de relaxamento, estratégias de coping e restruturação cognitiva.

Relativamente à actividade da doença, 7 estudos avaliaram este outcome; 1 demonstrou que a TCC seria prejudicial, 3 demonstraram não existir diferença entre esta e o controlo e 2 documentaram benefício. Destes, 2 estudos com dados completos foram incluídos na meta-análise, com um total de 506 doentes com CD e 188 com UC. A análise não demonstrou efeito significativo com o uso de TCC (SMD: 0.060; -0.449 e 0.568 CI 95%; p-values>0.818).

Todos os estudos avaliaram a depressão; 6 demonstraram não existir diferença entre esta e o controlo e 5 documentaram benefício. Destes, 3 estudos com dados completos foram

incluídos na meta-análise, com um total de 558 doentes. A análise não demonstrou efeito significativo com o uso de TCC (SMD: -0.131; -0.347, 0.084 CI 95%; p-values>0.233).

Setes estudos avaliaram síndromes ansiosas; 5 demonstraram não existir diferença entre esta e o controlo e 2 documentaram benefício. Destes, 3 estudos com dados completos foram incluídos na meta-análise, com um total de 558 doentes. A análise não demonstrou efeito significativo com o uso de TCC (SMD: -0.029; -0.232, 0.173 CI 95%; p-values>0.777).

Setes estudos avaliaram a qualidade de vida associada a doença; 3 demonstraram não existir diferença entre esta e o controlo e 4 documentaram benefício, um deles apenas num subgrupo de doentes (mais novos, com alta actividade de doença, recentemente diagnosticados, com más estratégias de coping e níveis altos de ansiedade e depressão no HADS). Destes, 3 estudos com dados completos foram incluídos na meta-análise, com um total de 558 doentes. A análise não demonstrou efeito significativo com o uso de TCC (SMD: 0.037; -0.178, 0.252 CI 95%; p-values>0.736).

Discussão e conclusão. Esta meta-análise falhou em provar benefícios da TCC nos doentes com DII nos 4 outcomes principais: actividade da doença, depressão, ansiedade e qualidade de vida, mas foram encontradas grandes limitações.

Como foi dito, as DII associam-se a incidências mais elevadas de perturbações psiquiátricas, como depressão e ansiedade e a TCC já mostrou benefícios em outras doenças gastrointestinais como a síndrome do cólon irritável; assim, era esperado que também tivessem sido obtidos resultados positivos para nos doentes com DII. É possível que as perturbações psiquiátricas nestes doentes tenham uma maior componente orgânica, o que é de particular relevância na actividade das DII.

Do total de 1012 doentes, apenas 594 foram incluídos na nossa análise de actividade de doença, e 558 para a depressão, ansiedade e qualidade de vida. Estudos futuros prescisam de um maior número de doentes, reportando dados completos.

Estudos em subgrupos demonstraram maior benefício da TCC; um estudo relatou benefício da TCC apenas num subgrupo de doentes (mais novos, com alta actividade de doença, recentemente diagnosticados, com más estratégias de coping e níveis altos de ansiedade e depressão no HADS), um em doentes com depressão subsindromática, outro

em doentes com qualidade de vida associada a saúde mental diminuída. O estudo de subgrupos deve ser avaliado no futuro.

Muitos estudos não relataram a actividade da doença, o que pode interferir com os resultados, como sugerido anteriormente. Adicionalmente, seria importante fazer a análise de doentes com CD e UC em separado, assim como ser reportada a terapêutica médica para a sua doença.

O benefício reportado foi, na maioria, apenas a curto prazo, perdendo-se no seguimento; assim, sessões adicionais poderiam ser benéficas.

As taxas de abandono foram, no geral, elevadas, o que se pode dever à exigência, nomeadamente de tempo, da TCC. Para contornar o problema, podem ser estudadas as componentes da TCC de que os doentes mais beneficiam, aplicando um tratamento mais curto e focados nesses achados. Adicionalmente, muitos outcomes têm sido relatados, o que implica um elevado número de questionários aplicados a estes doentes, o que pode aumentar a taxa de abandono; no futuro, sugerimos que sejam analisados a actividade da doença, depressão, ansiedade e qualidade de vida, sendo este último o de maior importância pois é o objectivo final de qualquer intervenção.

Nenhum estudo fez a análise de custos, que deverá passar a ser realizada.

Apesar de este estudo não ter demonstrado benefícios, acreditamos que, no futuro e seguindo as sugestões que apresentamos, resultados positivos possam surgir.